REMARKS

Status of the Claims

Claims 32-59 are pending in the present application. Claims 32, 37, 42, and 47 have been amended as suggested by the Examiner as described elsewhere herein. No new matter has been added by way of amendment.

The Examiner is respectfully requested to withdraw the rejections and allow claims 32-59. In any event, the Examiner is respectfully requested to enter the above amendments for purposes of further prosecution. The amendments were made pursuant to suggestions made by the Examiner.

The Rejection Under 35 U.S.C. § 101 Should be Withdrawn

Claims 32-59 under 35 U.S.C. § 101 were rejected on the grounds that the claimed invention is not supported by a specific asserted utility or a well-established utility. The rejection is respectfully traversed for the reasons described below.

The Examiner states that the claims are not rejected "under the grounds that 14926 could not encode a G-protein coupled receptor . . . but rather than at the time the application was filed, appellants have not provided a specific and substantial utility for the gene." December 14, 2001 Office Action, pages 3-4. The Examiner further states, "applicants do not provide a specific utility for the claimed '14926 receptor', as for example no ligand for the receptor and no specific function for the receptor are disclosed." December 14, 2001 Office Action, page 3. Thus, the rejection for lack of patentable utility is based on the premise that no utility asserted by the Applicants can be specific and substantial unless it depends in some way on the endogenous ligand or the physiologic function of the 14926 G-protein coupled receptor, and therefore the Examiner's burden of establishing a *prima facie* case of lack of utility may be met by demonstrating that the Applicants have not provided the endogenous ligand or physiologic function of the claimed receptor nucleotide sequence.

In fact, the Applicants have asserted specific, substantial utilities for the claimed invention that do not require a knowledge of either the endogenous ligand or the precise biological function of the 14926 receptor in order to be operable. These asserted utilities meet the requirements set forth in the statute, the applicable case law, and the utility examination guidelines.

Applicants have disclosed the sequence of a novel rhodopsin-family GPCR, and have demonstrated that the claimed 14926 nucleotide sequence is useful in screening for therapeutic compounds and in selectivity screening for drugs that bind specifically to a target GPCR but not to structurally-related receptors. Drugs that bind selectively to their molecular target are highly preferred over those that bind to structurally-related molecules, as selective compounds are far less likely to have unwanted side effects in clinical use. Because an important component of any drug development strategy is determining the selectivity of the drug for the molecular target of interest, the identification of the 14926 receptor provides an immediate benefit to the development of drugs targeting GPCRs. The usefulness of the 14926 receptor is not dependent on its biological role or ligand-binding properties, but comes instead from the fact that it shares a high level of sequence identity with an important class of drug targets.

Applicants have cited Goodwin *et al.* (2000) *Molecular Cell* 6:517-26 (provided herewith for the convenience of the Examiner as Appendix A) to demonstrate the role that orphan receptors play in screening for compounds that bind specifically to the target receptor but not to structurally-related receptors. *See,* pages 12-13 of Applicant's Amendment mailed October 3, 2001.

Applicants have also cited Stadel *et al.* (1997) *Trends in Pharmacological Science* 18:430-36 (provided herewith for the Examiner's convenience as Appendix B) to demonstrate that advances in molecular biology have led to dramatic changes in the way therapeutic compounds are identified. The Stadel *et al.* reference teaches that the availability of sequences encoding novel orphan GPCRs has led to a new pharmaceutical research paradigm based on a reverse molecular pharmacology approach to drug discovery. In the reverse molecular pharmacology approach, it is a full-length cloned receptor, rather than a ligand having an

unknown molecular target, that is the starting point of the drug discovery process. *See*, Figure 2 of Stadel *et al.*

In response to the Applicant's arguments, the Examiner quotes from the last paragraph of the first column of page 434 of Stadel *et al.*, where the authors state, "[t]he reverse molecular pharmacology strategy is a far more daunting challenge and risky endeavor when compared with the more traditional approach, since the starting material for a drug discovery effort is simply an orphan receptor of unknown function, with no apparent relationship to a disease indication." To put this statement in its proper context, however, one must consider the very next sentence of Stadel *et al.*, in which the authors state:

> the potential reward of using this approach is that resultant drugs naturally will be pioneer or innovative discoveries, and a significant proportion of these unique drugs may be useful to treat diseases for which existing therapies are lacking or insufficient.

Stadel *et al* at 434. Furthermore, when the Stadel *et al.* reference is considered in its entirety, it is clear that its primary teaching is not that the process of discovering drugs using a reverse molecular pharmacological approach is insurmountably difficult and should not be attempted, but rather that the reverse molecular pharmacological approach described is already being actively pursued because "the pharmaceutical industry has recognized the power of genomics to provide it with new and unique drug targets." Stadel *et al.* at 436. Thus, Applicants have demonstrated that those of skill in the art recognize the real-world utility of novel orphan GPCRs.

The Examiner argues that the use of the 14926 receptor sequence in drug screening and selectivity screening is not a specific utility because "it does not rely on a particular characteristic of the instant 14926 gene, but rather relies on features shared by many diverse GPCRs." (December 14, 2001 Office Action, page 5). This argument is at odds with the "Utility Examination Guidelines," which provide, "[w]hen a class of proteins is defined such that the members share a specific, substantial, and credible utility, the reasonable assignment of a new protein to the class of sufficiently conserved proteins would impute the same specific, substantial, and credible utility to the assigned protein." 66 Fed. Reg. 1092, 1097 (2001). This

statement from the "Utility Examination Guidelines" makes it clear that when a novel sequence is shown to encode a polypeptide belonging to a family of proteins that share a common utility, this supports the conclusion that the novel sequence has specific utility.

As further evidence that sequence identity with a class of proteins having a specific and substantial utility may be used to establish the specific and substantial utility of a polypeptide, Applicants cite Example 10 of the "Revised Interim Utility Guidelines Training Materials." Example 10 is directed to a nucleic acid encoding a polypeptide having a high level of sequence identity with DNA ligases. If the policy set forth in the Office Action as described above were followed, the polypeptide claimed in Example 10 of the "Revised Interim Utility Guidelines Training Materials" would be rejected for lack of utility because the well-established utility in this example is based on the claimed polypeptide's ligase activity and this utility is shared with all members of the ligase family of proteins. Instead, however, it is concluded in the analysis of this example that the claimed ligase has patentable utility. The patentable utility is demonstrated *because* the ligase can be used for the same purpose as other members of the ligase family of proteins, not in spite of this fact.

Similarly, Applicants have shown that the 14926 receptor is a member of a class of proteins, the rhodopsin subclass of GPCRs, that bind small molecules to mediate signal transduction pathways and have historically been among the most successful drug targets. *See*, Stadel *et al.* (1997) *Trends Pharmacological Science* 18 at 436. In fact, the 14926 receptor belongs to a family of receptors that are the target for more than 50% of all prescription drugs. Attwood (2001) *Trends Pharmacological Science* 22:162-65. Accordingly, the utilities asserted for the claimed 14926 GPCR in drug screening and selectivity screening are based on the unique biochemical activity shared by members of the rhodopsin family of GPCRs.

Example 10 of the "Revised Interim Utility Guidelines Training Materials" also demonstrates that the establishment of patentable utility does not require that the endogenous substrates and physiologic role of a polypeptide be known if the asserted or well-established utilities are operable without this knowledge. In Example 10, the well-established utility of the claimed polypeptide is based on its *in vitro* biochemical activity. According to the analysis in the example, "DNA ligases have a well-established use in the molecular biology art based on this

class of protein's ability to ligate DNA ("Revised Interim Utility Guidelines Training Materials," March 1, 2000, page 54). Thus, because the utility of the claimed ligase nucleotide sequence is well-established in molecular biology, the endogenous substrates and biological role of the ligase in the cells in which it is expressed are not required to establish utility. Similarly, the well-established utility of the 14926 GPCR in drug development is based on its biochemical activity, *i.e.* its G-protein-mediated signal transduction activity. Just as the biochemical activity of the ligase of Example 10 confers patentable utility to this protein in the absence of its physiologic substrates or utility, the biochemical activity of the 14926 receptor confers patentable utility to this receptor in the absence of its specific ligands or physiologic function.

The Examiner argues that utilities asserted by the Applicants "constitute an invitation to experiment and an invitation to use the gene and encoded protein as a research tool." (December 14, Office Action, pages 4 and 5). The argument that an asserted utility as a research tool is not sufficient to satisfy the utility requirement of 35 U.S.C. § 101 is contrary to the provisions set forth in the eighth edition of the *Manual of Patent Examination Procedure*, which states that inventions should not be rejected for lack of utility merely because they are to be used in a research or laboratory setting. The *Manual of Patent Examination Procedure* provides:

> confusion can result when one attempts to label certain types of inventions as not being capable of having a specific and substantial utility based on the setting in which the invention is to be used. One example is inventions to be used in a research or laboratory setting. Many research tools such as gas chromatographs, *screening assays*, and nucleotide sequencing techniques have a clear, specific, and unquestionable utility (e.g. they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact "useful" in a patent sense.

Manual of Patent Examination Procedure § 2107.01 (8th ed. 2001), emphasis added.

Accordingly, Applicant's asserted utilities for the 14926 receptor in drug screening and selectivity screening are not insubstantial or non-specific merely because these utilities are operable in a laboratory setting. Furthermore, no additional research is required to confirm that the 14926 receptor has utility in drug screening and selectivity screening. Applicants have

demonstrated that the 14926 receptor is a member of the rhodopsin family of GPCRs, a family of cell membrane receptors that bind small molecules to mediate signal transduction pathways and have historically been among the most successful drug targets. Because of these properties, which are unique to rhodopsin family G-protein coupled receptors, those of skill in the art recognize that the identification of novel orphan rhodopsin family G-protein coupled receptors has real-world value in the pharmaceutical research field as a tool in drug screening and selectivity screening, even in the absence of experimental evidence demonstrating the 14926 receptor ligand or physiologic function.

The USPTO "Utility Examination Guidelines" state, "[a]n applicant need only provide one credible assertion of specific and substantial utility for each claimed invention to satisfy the utility requirement." 66 Fed. Reg. 1092, 1098 (2001). This regulation is consistent with *Cross v. Iizuka*, 753 F.2d 1040 (Fed. Cir. 1985) in which the court held that "[w]hen a properly claimed invention meets at least one stated objective, utility under §101 is clearly shown." Thus, the Examiner's utility rejection must necessarily depend on the invalidity of each of Applicant's asserted uses.

The PTO guidelines state, "[a] rejection based on lack of utility should not be maintained if an asserted utility for the claimed invention would be considered specific, substantial, and credible by a person of ordinary skill in the art in view of all evidence of record" 66 Fed. Reg. at 1098. Further, the guidelines state, "[c]redibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record...that is probative of the applicant's assertions." *Id.* Applicants have demonstrated that one of ordinary skill in the art would find the present invention useful for selectivity screening of compounds that target rhodopsin family GPCRs as described above and thus the utility standard is met.

The USPTO utility examination guidelines state,

> [w]here the asserted utility is not specific or substantial, a *prima facie* showing [of no specific and substantial credible utility] must establish that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the applicant would be specific and substantial. The *prima facie* showing must contain the following elements: (1) An explanation that clearly sets

> forth the reasoning used in concluding that the asserted utility for the claimed is not both specific and substantial nor well-established; (2) Support for factual findings relied upon in reaching this conclusion; and (3) An evaluation of all relevant evidence of record, including utilities taught in the closest prior art.

Id. Further, "[o]ffice personnel are reminded that they must treat as true a statement of fact made by an applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. *Id.*

In the present case, a *prima facie* case of no utility has not been presented. No evidence has been presented to rebut Applicant's assertion that the 14926, as a member of the rhodopsin family of GPCRs, is useful in drug screening and selectivity screening. Instead, the Examiner argues that Applicants must provide evidence identifying the 14926 receptor ligand or physiologic function in order to satisfy the utility requirement under 35 U.S.C. § 101 and refuses to accept the specific, substantial, and credible utilities asserted by the Applicants despite the fact that these asserted utilities do not require a knowledge of the 14926 ligand or physiologic function in order to be operable.

In view of the above arguments, all grounds for rejection under 35 U.S.C. § 101 have been overcome. Reconsideration and withdrawal of the rejection are therefore respectfully requested.

The Rejections Under 35 U.S.C. § 112, First Paragraph, Should be Withdrawn

Claims 32-59 were rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the claimed invention is not supported by either a specific asserted utility or a well-established utility and therefore one of skill in the art would not know how to use it. The rejection is respectfully traversed on the grounds that Applicants have provided a specific, substantial, and credible utility for the claimed invention as described above; therefore one of skill in the art would know how to use it.

The Examiner has rejected claims 52, 54, 56, and 58 and their dependent claims under 35 U.S.C. § 112, first paragraph, on the grounds that these claims recite a step of determining whether a test compound modulates the activity of a 14926 polypeptide but have not disclosed which activity to measure. The rejection is respectfully traversed. The specification describes, on line 28 of page 7 through line 23 of page 9, G-protein mediated signaling pathways, including pathways mediated by phophatidylinositol turnover and pathways mediated by cyclic AMP turnover and metabolism. Methods for assaying these signal transduction pathways are well known in the art. *See*, for example, Kenakin (1996) *Pharmacol. Rev.* 48:413-63.; and Filtz *et al.* (1994) *Mol. Pharmacol.* 46:8-14, provided herewith for the convenience of the Examiner as Appendices C and D. Accordingly, based on the guidance provided in the specification, one of skill in the art would be able to determine whether a test compound modulates the activity of a 14926 polypeptide.

Claims 37-46 and 54-57 were rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the specification does not provide a sufficient written description of the polypeptides used in the claimed methods. This rejection is respectfully traversed for the reasons described below.

The Examiner argues that in order to provide sufficient written description of the claimed sequence variants, Applicants must disclose each mutation or substitution that may be made without affecting the activity of the 14926 polypeptide. However, this requirement is not supported by the "Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, 'Written Description' Requirement" (66 Fed. Reg. 1099 (2001)) and the supporting case law.

The "Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, 'Written Description' Requirement" state that genus may be described by "sufficient description of a representative number of species . . . or by disclosure of relevant, identifying characteristics , *i.e.* structure or other physical and/or chemical properties." *Id.* at 1106. Furthermore, the Guidelines state that "[d]isclosure of any combination of . . . identifying characteristics that distinguish the claimed invention from other materials and would lead one to the conclusion that

the applicant was in possession" of the claimed invention is sufficient to satisfy the written description requirement. *Id.* at 1106.

Applicants submit that the written description provided for the polypeptides recited in claims 37-46 and 54-57 meet this requirement. The claims recite the identifying structural characteristics that define each genus of nucleotide sequences or amino acid sequences. Claims 37 and 54 recite polypeptides comprising an amino acid sequence having at least 70, 80%, or 90% sequence identity with amino acid sequence shown in SEQ ID NO:2. Claims 42 and 56 recite polypeptides comprising the amino acid sequence of a sequence variant of the amino acid sequence shown in SEQ ID NO:1, where the sequence variant is encoded by a nucleotide sequence that hybridizes to the nucleotide sequence shown in SEQ ID NO:2 under the specified stringent conditions. The structural limitations in these claims are sufficient to distinguish the claimed nucleotide sequences and amino acid sequences from other materials and thus sufficiently define the claimed genus.

Furthermore, in *Regents of the University of California v. Eli Lilly & Co*, 119 F.3d 1559, 1569 (Fed. Cir. 1997), the court held that "[a] description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." The recitation of the structural features of sequence identity with SEQ ID NO:1 or hybridization under stringent conditions with SEQ ID NO:2 is sufficient to satisfy this requirement.

An Applicant may also rely upon functional characteristics in the description, provided there is a correlation between the function and structure of the claimed invention. *Id.* at 1568. In addition to reciting the identifying structural features of the claimed genus, claims 37, 42, 54, and 56 recite the distinguishing functional characteristics of the genus. Claims 37, 42, 54, 56, and their dependent claims are drawn to a genus of polypeptides having G-protein mediated signal transduction activity. Accordingly, each genus recited in claims 37-46 and 54-57 has been described by both its structural and functional features.

Example 14 of the "Written Description Training Materials" demonstrates that when the structural and functional features of the sequences encompassed by a genus are described, the

description of the genus meets the requirements of 35 U.S.C. § 112, first paragraph. Example 14 is directed to a genus of proteins having at least 95% sequence identity to the sequence of SEQ ID NO:3, wherein the proteins in the genus catalyze the reaction A → B. The conclusion in the analysis of this example is that the generic claim of Example 14 is sufficiently described under § 112, first paragraph, because (1) "the single sequence disclosed in SEQ ID NO:3 is representative of the genus" and (2) the claim recites a limitation requiring the compound to catalyze the reaction from A → B. The conclusion in the Training Materials is that one of skill in art would recognize that the applicants were in possession of the necessary common attributes possessed by the members of the genus.

Following the analysis of Example 14 of the Training materials, claims 37-46 and 54-57 satisfy the written description requirements of § 112, first paragraph. As in Example 14, the structural and functional features of the sequences falling within the genus are described, and thus one of skill in the art would recognize that the Applicants were in possession of the claimed invention.

In view of the above arguments, all grounds for rejection under 35 U.S.C. § 112, first paragraph, have been overcome. Accordingly, reconsideration and withdrawal of the rejections are respectfully requested.

The Rejection Under 35 U.S.C. § 112, Second Paragraph Should be Withdrawn

Claims 32, 37, 42, and 47 have been rejected under 35 U.S.C. § 112, second paragraph on the grounds that they recite a method step of "contacting the polypeptide with a compound under conditions that allow the compound to modulate the activity of the polypeptide to thereby modulate the activity of the polypeptide." Applicants believe that one of skill in the art would understand that the rejected language describes the conditions under which the method step is carried out (*i.e.*, conditions that allow the compound to modulate the activity of the polypeptide) and the intended result of the method step (*i.e.*, the modulation of the activity of the polypeptide). Nevertheless, claims 32, 37, 42, and 47 have been amended to remove the reference to the intended result of the method step, thereby obviating the rejection.

Claim 37 is rejected under 35 U.S.C. § 112, first paragraph, on the grounds that it is indefinite for reciting the language" the polypeptide is modulated is in a cell." Applicants agree that the claim as written is confusing and have amended claim 37 to fix the error noted by the Examiner.

In view of these amendments, all grounds for rejection under 35 U.S.C.§ 112, second paragraph have been obviated. Accordingly, reconsideration and withdrawal of the rejections are respectfully requested.

CONCLUSIONS

It is believed that all the rejections have been obviated or overcome and the claims are in conditions for allowance. Early notice to this effect is solicited.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those, which may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR §1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: **BOX AF**, Commissioner for Patents, Washington, DC 20231, on March 13, 2002.

Nora C. Martinez

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Version with Markings to Show Changes Made:

Please amend claims 32, 37, 42, and 47 as follows:

32. (Amended) A method for modulating the activity of a polypeptide comprising the amino acid sequence shown in SEQ ID NO:1; the method comprising contacting the polypeptide with a compound under conditions that allow the compound to modulate the activity of the polypeptide[to thereby modulate the activity of the polypeptide], wherein the activity of the polypeptide is modulated in a cell selected from the group consisting of brain cells, spleen cells, lung cells, kidney cells, skeletal muscle cells, liver cells, and heart cells.

37. (Amended) A method for modulating the activity of a polypeptide comprising an amino acid selected from the group consisting of:

(a) the amino acid sequence of a sequence variant of the amino acid sequence shown in SEQ ID NO:1, wherein said sequence variant has G-protein mediated signal transduction activity and has at least about 70% sequence identity with the amino acid sequence shown in SEQ ID NO:1;

(b) the amino acid sequence of a sequence variant of the amino acid sequence shown in SEQ ID NO:1, wherein said sequence variant has G-protein mediated signal transduction activity and has at least about 80% sequence identity with the amino acid sequence shown in SEQ ID NO:1;

(c) the amino acid sequence of a sequence variant of the amino acid sequence shown in SEQ ID NO:1, wherein said sequence variant has G-protein mediated signal transduction activity and has at least about 90% sequence identity with the amino acid sequence shown in SEQ ID NO:1;

the method comprising contacting the polypeptide with a compound under conditions that allow the compound to modulate the activity of the polypeptide[to thereby modulate the activity of the polypeptide], wherein the activity of the polypeptide is modulated [is]in a cell selected from the

group consisting of brain cells, spleen cells, lung cells, kidney cells, skeletal muscle cells, liver cells, and heart cells.

42. (Amended) A method for modulating the activity of a polypeptide comprising the amino acid sequence of a sequence variant of the amino acid sequence shown in SEQ ID NO:1, wherein said sequence variant has G-protein mediated signal transduction activity and is encoded by a nucleotide sequence that hybridizes to the nucleotide sequence shown in SEQ ID NO:2 under stringent conditions comprising hybridization in 6X SSC at about 45°C followed by one or more washes in 0.2X SSC/0.1%SDS at 50-65°C; said method comprising contacting the polypeptide with a compound under conditions that allow the compound to modulate the activity of the polypeptide[to thereby modulate the activity of the polypeptide], wherein said modulation is in a cell selected from the group consisting of brain cells, spleen cells, lung cells, kidney cells, skeletal muscle cells, liver cells, and heart cells.

47. (Amended) A method for modulating the activity of a polypeptide comprising the amino acid sequence set forth as amino acids 6 to 370 of SEQ ID NO:1; said method comprising contacting the polypeptide with a compound under conditions that allow the compound to modulate the activity of the polypeptide[to thereby modulate the activity of the polypeptide], wherein said modulation is in a cell selected from the group consisting of brain cells, spleen cells, lung cells, kidney cells, skeletal muscle cells, liver cells, and heart cells.